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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,744	10/05/2001	Marcel P. Bruchez	IVGN 620	4380

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EXAMINER	
JUNG, UNSU	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/972,744	BRUCHEZ ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,11-14,16-20,25-35,38,74-79 and 109* is/are pending in the application.

4a) Of the above claim(s) *16-20, 25-35, and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-14,74-79 and 109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner for the current application has been changed from Pensee Do to Unsu Jung in Art Unit 1641. Any inquiry concerning this application should be directed to Unsu Jung, whose contact information is provided in the conclusion section of this Office Action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 30, 2007 has been entered. The submission included amendments to claims 1-5, 11, 74, 75, 78, cancellation of claim 6, and addition of new claim 109.

3. Claims 1-5, 11-14, 16-20, 25-35, 38, 74-79, and 109 are pending, claims 16-20, 25-35, and 38 have been withdrawn from consideration, and claims 1-5, 11-14, 74-79, and 109 are under consideration for their merits.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on May 30, 2007 has been considered by the examiner. Further, relevant page numbers (pp410-417) for citation No. C6 has been included as indicated on the IDS.

Rejections Withdrawn

5. Applicant's arguments, see pp9-10, filed on May 30, 2007, with respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Millard (U.S. Patent No. 5,534,416, July 9, 1996) in view of Bawendi (U.S. Patent No. 6,306,610, filed on Sept. 17, 1999) have been fully considered and are persuasive. The rejection of claims 1-6, 11-14, 74, and 75 under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi has been withdrawn. Subsequently, the following rejections have been also withdrawn:

- Rejection of claim 76 under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi, and further in view of Rothbard (U.S. Patent No. 6,306,993, filed on May 21, 1998) and in view of Sodroski et al. (U.S. Patent No. 6,761,902, filed on Dec. 27, 2000);
- Rejection of claim 77 under 35 U.S.C. 103(a) as being unpatentable over Milliard in view of Bawendi, and further in view of Rothbard
- Rejection of claim 78 under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi et al., and further in view of Frankel et al. (U.S. Patent No. 5,652, 122, July 29, 1997).

- Rejection of claim 79 under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi, and further in view of Barbera-Guillem (U.S. Patent No. 6,194,213, published on Feb. 27, 2001 and filed on Dec. 10, 1999).

It is further noted that there was a typo in U.S. Patent No. for Frankel et al. reference on p7, line 3, wherein the U.S. Patent No. for Frankel et al. reference should be corrected to 5,652,122.

Specification

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks (For example, Cascade Blue®, BODIPY™, CY®, Texas Red®, and others listed in Table 1, on pp23-27) should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: composition of claim 74, wherein the translocatable molecule is a cationic polymer consisting of 5 to 25 contiguous Lys and/or Arg residues.

Applicant's amendment filed on May 30, 2007 directs support to Fig. 17 and description, the Examples, particularly Ex. 7, and page 6, last paragraph, page 9, 3rd paragraph, page 20, page 48-55, particularly page 49, 1st paragraph, page 57, 2nd paragraph, and page 59, 1st paragraph of the specification, among others.

Although, the specification discloses that polycationic substances such as poly-L-lysine can be included in the semiconductor nanocrystal for encoding cells (p48, line 7), the specification fails to disclose specific length of the poly-L-lysine. Further, the specification is does not disclose a cationic polymer consisting of 5 to 25 contiguous Arg residues and 5 to 25 contiguous Lys and Arg residues.

The specification as filed does not provide a written description or set forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as

they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the "cationic polymer consisting of 5 to 25 contiguous Lys and/or Arg residues" indicated above.

See MPEP 714.02 and 2163.06.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: structural relationship between encoded cells and semiconductor nanocrystals of the composition

and porogen/liposome. It is unclear how the porogen/liposome is structurally related to either the encoded cells or the semiconductor nanocrystals. Therefore, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention so that one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-5, 11-14, 74, 75, and 109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) in view of Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018).

Walt et al. teaches a biosensor array of a monoculture living cells or randomly mixed populations of living cells (see entire document particularly column 5, line 65-column 6, line 20). A unique feature of the biosensor array is that the cells within each population are individually encoded (a composition comprising a plurality of separately detectable encoded cells) for maintaining cell identity within the array when randomly mixed populations of cells are employed (column 15, lines 15-42). Cells may be encoded with a single fluorophore or chromophore dye or ratios of such dyes (column 15, lines 19-20). Cells may be encoded by injecting a non-toxic fluorescing compound into the cell cytoplasm (column 15, lines 20-22). A wide variety of fluorophores, chromophores, stains or a dye compounds may be used for encoding cells (column 15, lines 43-62). Encoding dyes may be permeant or impermeant to the cell membrane (column 15, lines 44-45). Impermeant dyes may be conjugated with acetoxymethyl ester to allow take up by cells (column 15, lines 46-47). Further, cell organelle dye

probes may be employed for encoding (column 15, lines 59-60). Encoding cells thus provide for rapid, simultaneous measurements of all cells and cell populations within the array without the need to mechanically scan the array to acquire a series of sequential measurements for each cell (column 16, lines 4-27).

With respect to claim 2, Walt et al. teaches that the cells are prokaryotic (*E. Coli*, column 12, lines 31-57).

With respect to claim 3, Walt et al. teaches that the cells are eukaryotic (mouse and human cells, column 12, lines 31-57 and column 26, lines 8-14).

With respect to claim 4, Walt et al. teaches that the cells are selected from the group consisting of yeast cells, mammalian cells, and plant cells (column 12, lines 31-57).

With respect to claim 5, Walt et al. teaches that the cells are mammalian cells selected from the group consisting of a human cell, a mouse cell, and a rat cell (column 12, lines 31-57 and column 26, lines 8-14; and column 27, lines 59-67).

However, Walt et al. fails to teach a composition, wherein the cells are encoded with semiconductor nanocrystals.

According to the specification on p11, lines 4-9, the terms "semiconductor nanocrystal," "quantum dot" and "Qdot™ nanocrystal" are used interchangeably herein to refer to semiconductor nanoparticles composed of an inorganic crystalline material that is luminescent (i.e., they are capable of emitting electromagnetic radiation upon excitation), and include an inner core of one or more first semiconductor materials that

is optionally contained within an overcoating or "shell" of a second semiconductor material.

Chan et al. teaches highly luminescent semiconductor quantum dots (semiconductor nanocrystals), which are biocompatible and are suitable for use in cell biology and immunoassays (see entire document, particularly Abstract). The advantages of using semiconductor quantum dots/nanocrystals over the conventional organic fluorescent dyes are well known in the art. The advantages include resistance to photobleaching and enhanced quantum yield (p2017, Fig. 3 and 3rd column). The improved photostability of the semiconductor quantum dots/nanocrystals would allow real-time observations of molecular trafficking in living cells (p2017, 2nd column, last paragraph). Further, sufficiently monodispersed semiconductor quantum dots/nanocrystals would allow use in multiplex detection schemes (p2017, 2nd column, last paragraph).

With respect to claim 11, Chan et al. teaches semiconductor nanocrystals comprising a core and a shell (Fig. 1).

With respect to claims 12-14, Chan et al. teaches a semiconductor nanocrystals comprising CdSe core and ZnS shell (Fig. 1).

With respect to claim 74, Chan et al. teaches semiconductor nanocrystal conjugated to a translocatable molecule (transferrin, p2018, 1st column).

With respect to claim 75, Chan et al. teaches a semiconductor nanocrystal conjugated to a translocatable molecule (transferrin), which is a ligand for a cellular receptor that enters cells by endocytosis (p2018, 1st column).

With respect to claim 109, Chan et al. teaches that cells can be encoded with a plurality of distinct semiconductor nanocrystals (p2017, 2nd column, last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the organic (fluorophore/chromophore) dyes of Walt et al. with the semiconductor quantum dots/nanocrystals of Chan et al. to encode the cells in the composition of Walt et al. As disclosed in Chan et al., the motivation for the combination would be to use encoding labels with advantages of having resistance to photobleaching and enhanced quantum yield compared to the conventional organic dyes. Further, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in substituting the organic (fluorophore/chromophore) dyes of Walt et al. with the semiconductor quantum dots/nanocrystals of Chan et al. since Chan et al. teaches that the semiconductor quantum dots/nanocrystals would allow real-time observations of living cells.

15. Claims 76 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) in view of Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) as applied to claims 1 and 74 above, and further in view of Boucher, Jr. et al. (U.S. PG Pub. No. US 2003/0004123 A1, filed on Dec. 23, 1998).

Walt et al. in view of Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 14 above. Although Walt et al. in view of Chan et al. teaches that cells may be

encoded with semiconductor nanocrystals, which can be taken up by cells as set forth above in item 14, Walt et al. in view of Chan et al. fails to specifically teach a composition, wherein the cells comprising a semiconductor nanocrystals conjugated to a ligand for a G-protein coupled receptor (GPCR).

Boucher, Jr. et al. teaches a method of internalizing a fluorescent label conjugated to a $P2Y_2$ receptor ($P2Y_2$-R) ligand (GPCR ligand) via $P2Y_2$-R (GPCR, see entire document, particularly p17, paragraph [0302]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ a GPCR ligand of Boucher, Jr. et al. as the biomolecule coupled to the semiconductor nanocrystals of Walt et al. in view of Chan et al. in order to encode cells via cellular uptake of encoding labels as taught by Boucher, Jr. et al. Using the known technique of conjugating a GPCR ligand to a label to provide cellular uptake of the encoding labels would have been obvious to one of ordinary skill in the art. Further, one of ordinary skill in the art would have had a reasonable expectation of success in employing a GPCR ligand of Boucher, Jr. et al. as the biomolecule coupled to the semiconductor nanocrystals of Walt et al. in view of Chan et al. since Walt et al. teaches that variety of cells including epithelial cells can be used in the composition (column 28, lines 58-65) and Boucher, Jr. et al. teaches that $P2Y_2$-R is expressed by airway epithelial cells (p635, 1st column, 2nd paragraph).

With respect to claim 77, Walt et al. in view of Chan et al. and Boucher, Jr. et al. teaches a transporter ligand ($P2Y_2$-R ligand) conjugated to a semiconductor nanocrystals.

16. Claim 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) in view of Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) as applied to claims 1 and 74 above, and further in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998).

Walt et al. in view of Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 14 above. Although Walt et al. in view of Chan et al. teaches that cells may be encoded with semiconductor nanocrystals, which can be taken up by cells as set forth above in item 14, Walt et al. in view of Chan et al. fails to specifically teach a composition, wherein the cells comprising a semiconductor nanocrystals conjugated to a cationic polymer consisting of 5 to 25 contiguous Lysine (Lys) and/or Arginine (Arg) residues.

Rothbard et al. teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent that is covalently attached to a transport polymer (translocatable molecule, see entire document). Such transport polymer has 5 to 25 subunits of Lys or Arg (see SEQ ID NO:'s 2, 3-11 and 13-17). The transport enhancing polymers are exemplified by peptides in which Lys or Arg residues constitute the subunits (see SEQ ID NO:'s 2, 3-11 and 13-17). Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant

cells and the like (column 3, lines 17-25). The conjugate is effective to enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate macromolecules along (see column 6, line 63-column 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag (see column 11, lines 3-4). Fluorescently labeled peptide polymers composed of 6 or more Arginine residues entered cells more efficiently than the tat sequence 49-57 in Fig. 1 (see column 11, lines 30-40).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ a cationic polymer consisting of 5 to 25 contiguous Lys or Arg as taught by Rothbard et al. coupled to the semiconductor nanocrystals of Walt et al. in view of Chan et al. in order to encode cells via cellular uptake of encoding labels. Using the known technique of conjugating a cationic polymer consisting of 5 to 25 contiguous Lys or Arg to a label to provide cellular uptake of the encoding labels would have been obvious to one of ordinary skill in the art. Further, one of ordinary skill in the art would have had a reasonable expectation of success in employing a cationic polymer consisting of 5 to 25 contiguous Lys or Arg of Rothbard et al. as the biomolecule coupled to the semiconductor nanocrystals of Walt et al. in view of Chan et al. since Walt et al. teaches that variety of cells including eukaryotic and prokaryotic cells can be used in the composition (column 28, lines 58-65) and Rothbard et al. teaches that cationic polymer consisting of 5 to 25 contiguous Lys or Arg can be used for transport of conjugates across the biological membrane of eukaryotic and prokaryotic cells.

17. Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) in view of Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) as applied to claims 1 and 74 above, and further in view of Lee et al. (U.S. Patent No. 5,643,599, July 1, 1997).

Walt et al. in view of Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 14 above. However, Walt et al. in view of Chan et al. fails to specifically teach a composition further comprising a porogen or liposome.

Lee et al. teaches a method of using liposome to facilitate delivery of an extracellular agent to the cytoplasm of target cells (see entire document, particularly Abstract). Liposomes are vesicles with an aqueous interior enclosed by one or more phospholipid bilayers (column 1, lines 21-22). Such vesicles have demonstrated utility as vehicles for delivering agents to target tissues or organs (column 1, lines 22-24). The liposomes of Lee et al. include an agent delivery enhancer, which facilitates transport of the extracellular agents from the phagocytosed liposomes to the target cell cytoplasm (column 2, lines 37-42). As a result, the liposome of Lee et al. advantageously offers compositions and methods for delivering to virtually any type of cell that is capable of internalizing a liposome, higher effective concentrations of extracellular agents in the cytoplasm of target cells than previously achieved (column 2, lines 42-47).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include semiconductor nanocrystals of Walt et al. in view of Chan et al. in the liposome of Lee et al. in order to deliver semiconductor nanocrystals to the cytoplasm of cells to be encoded. The advantage of using a delivery agent such as liposomes, which are capable of delivering high effective concentrations of extracellular agents to the cytoplasm of virtually any type of target cells provides the motivation to combine teachings of Walt et al. in view of Chan et al. and Lee et al. Further, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the semiconductor nanocrystals of Walt et al. in view of Chan et al. in the liposome of Lee et al. since Lee et al. teaches that extracellular agents can be effectively delivered to virtually any type of cell that is capable of internalizing a liposome.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Copending Application No. 11/682,063

A. Claims 1-5, 11-14, 74, 75, and 109 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/682,063 in view of Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) and Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018).

The claims of the copending Application recites a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals. However, the copending Application is silent on reciting that the semiconductor nanocrystals are localized in the cytoplasm, nucleus, or an organelle of the cells.

Walt et al. teaches a biosensor array of a monoculture living cells or randomly mixed populations of living cells as set forth in item 14 above.

Chan et al. teaches highly luminescent semiconductor quantum dots (semiconductor nanocrystals), which are biocompatible and are suitable for intracellular labeling of living cells as set forth in item 14 above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to encode the cells of the copending Application

intracellularly in cytoplasm or organelles of the cells as taught by Walt et al. in order to encode the cells. As disclosed in Walt et al., the motivation for the combination would be to use encoded cells for maintaining cell identity within the array of randomly mixed populations of cells for rapid and simultaneous measurements of all cells. Further, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in encoding the cells of the copending Application intracellularly in cytoplasm or organelles of the cells since Chan et al. teaches that intracellular labeling of cells with the semiconductor quantum dots/nanocrystals would allow real-time observations of living cells.

This is a provisional obviousness-type double patenting rejection.

B. Claims 76 and 77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/682,063 in view of Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) and Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) as applied to claims 1 and 74 above, and further in view of Boucher, Jr. et al. (U.S. PG Pub. No. US 2003/0004123 A1, filed on Dec. 23, 1998).

The copending Application in view of Walt et al. and Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 19A above. Although the

copending Application in view of Walt et al. and Chan et al. teaches that cells may be encoded with semiconductor nanocrystals, which can be taken up by cells as set forth above in item 19A, the copending Application in view of Walt et al. and Chan et al. fails to specifically teach a composition, wherein the cells comprising a semiconductor nanocrystals conjugated to a ligand for a G-protein coupled receptor (GPCR).

Boucher, Jr. et al. teaches a method of internalizing a fluorescent label conjugated to a $P2Y_2$ receptor ($P2Y_2$-R) ligand (GPCR ligand) via $P2Y_2$-R as set forth in item 15 above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ a GPCR ligand of Boucher, Jr. et al. as the biomolecule coupled to the semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. in order to encode cells via cellular uptake of encoding labels as taught by Boucher, Jr. et al. Using the known technique of conjugating a GPCR ligand to a label to provide cellular uptake of the encoding labels would have been obvious to one of ordinary skill in the art. Further, one of ordinary skill in the art would have had a reasonable expectation of success in employing a GPCR ligand of Boucher, Jr. et al. as the biomolecule coupled to the semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. since Walt et al. teaches that variety of cells including epithelial cells can be used in the composition (column

28, lines 58-65) and Boucher, Jr. et al. teaches that $P2Y_2$-R is expressed by airway epithelial cells (p635, 1st column, 2nd paragraph).

This is a provisional obviousness-type double patenting rejection.

C. Claim 78 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/682,063 in view of Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) and Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) as applied to claims 1 and 74 above, and further in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on September 14, 1999).

The copending Application in view of Walt et al. and Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 19A above. Although the copending Application in view of Walt et al. and Chan et al. teaches that cells may be encoded with semiconductor nanocrystals, which can be taken up by cells as set forth above in item 19A, the copending Application in view of Walt et al. and Chan et al. fails to specifically teach a composition, wherein the cells comprising a semiconductor nanocrystals conjugated to a cationic polymer consisting of 5 to 25 contiguous Lysine (Lys) and/or Arginine (Arg) residues.

Rothbard et al. teaches methods and composition for transporting drugs and macromolecules across biological membranes using transport enhancing polymers as set forth in item 16 above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ a cationic polymer consisting of 5 to 25 contiguous Lys or Arg as taught by Rothbard et al. coupled to the semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. in order to encode cells via cellular uptake of encoding labels. Using the known technique of conjugating a cationic polymer consisting of 5 to 25 contiguous Lys or Arg to a label to provide cellular uptake of the encoding labels would have been obvious to one of ordinary skill in the art. Further, one of ordinary skill in the art would have had a reasonable expectation of success in employing a cationic polymer consisting of 5 to 25 contiguous Lys or Arg of Rothbard et al. as the biomolecule coupled to the semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. since Walt et al. teaches that variety of cells including eukaryotic and prokaryotic cells can be used in the composition (column 28, lines 58-65) and Rothbard et al. teaches that cationic polymer consisting of 5 to 25 contiguous Lys or Arg can be used for transport of conjugates across the biological membrane of eukaryotic and prokaryotic cells.

This is a provisional obviousness-type double patenting rejection.

D. Claim 79 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/682,063 in view of Walt et al. (U.S. Patent No. 6,210,910, filed on Mar. 2, 1998) and Chan et al. (*Science*, 1998, Vol. 281,

pp2016-2018) as applied to claims 1 and 74 above, and further in view of Lee et al. (U.S. Patent No. 5,643,599, July 1, 1997).

The copending Application in view of Walt et al. and Chan et al. teaches a composition comprising a plurality of separately detectable cells encoded with semiconductor nanocrystals as set forth in item 19A above. However, the copending Application in view of Walt et al. and Chan et al. fails to specifically teach a composition further comprising a porogen or liposome.

Lee et al. teaches a method of using liposome to facilitate delivery of an extracellular agent to the cytoplasm of target cells as set forth in item 17 above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. in the liposome of Lee et al. in order to deliver semiconductor nanocrystals to the cytoplasm of cells to be encoded. The advantage of using a delivery agent such as liposomes, which are capable of delivering high effective concentrations of extracellular agents to the cytoplasm of virtually any type of target cells, provides the motivation to combine teachings of the copending Application in view of Walt et al. and Chan et al. and Lee et al. Further, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the semiconductor nanocrystals of the copending Application in view of Walt et al. and Chan et al. in the liposome of Lee et al. since Lee et al. teaches that

extracellular agents can be effectively delivered to virtually any type of cell that is capable of internalizing a liposome.

This is a provisional obviousness-type double patenting rejection.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
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